Polymer International 46 (1998) 196–202

Effects of Residual Monomer on the Degradation of DL-Lactide Polymer

S.-H. Hyon,* K. Jamshidi & Y. Ikada

Research Center for Biomedical Engineering, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606, Japan

(Received 3 June 1997; accepted 16 September 1997)

Abstract: The effects of remaining monomer on hydrolysis of poly(DL-lactide) were examined by adding different amounts of monomer to purified polymer samples. The existence of monomer in the polymerization products was found to enhance hydrolytic degradation of the polymer. A porous texture was observed on the SEM photographs of degraded materials, which led to the conclusion that the remaining monomer enabled water molecules to gain better access to the polymer matrix through this porous structure. The effects of molecular weight and chemical composition of polylactides on the hydrolytic degradation were also studied. Poly(DL-lactic acid) with higher molecular weights showed longer retention of the initial properties such as molecular weight and tensile strength. Copolymerization of DL-lactide with glycolide enhanced the hydrolysis, probably because of increased hydrophilicity of the polymers. © 1998 SCI.

Polym. Int. 46, 196–202 (1998)

Key words: biodegradable polymer, poly(DL-lactide), residual monomer, DL-lactide–glycolide copolymer, hydrolysis

INTRODUCTION

In the past decades biodegradable polymers have attracted much attention in both industrial and medical applications. Among them, polyesters of α-hydroxy aliphatic acids have been most extensively studied with respect to their synthesis, physical properties, biodegradation and applications. As a consequence, polyesters synthesized from glycolide and lactides, and their copolyesters have already been used practically in surgery, pharmaceutics and the plastic industry, although their market size is still limited.

Many people seem to think that most of the major problems associated with these aliphatic poly(α-hydroxy acid)s have already been solved because a large number of investigations have been published concerning these polyesters.[1–14] However, this is not true with respect to not only their synthesis, but also their physicochemical properties and biodegradation. For instance, biodegradation of polyesters is influenced by a number of factors including polymer molecular weight, crystallinity, chemical composition, sample size, purity, additives, medium pH, temperature and so on, but few of them have been the subject of detailed studies. To control the biodegradation of these polymers, it is essential to make clear the effects of all these influencing factors on the degradation.[15–24]

The objective of this study is to present results concerning the effects of a small amount of monomer remaining in the polymerization product on the degradation of the resulting polyester. We selected DL-lactide polymer (PDLLA) as a biodegradable polyester, because PDLLA is an entirely amorphous polyester with the simplest chemical structure. Such an amorphous polymer has a single-phase structure, in contrast with a crystalline polymer consisting of amorphous and crystalline phases. When a polymer is used on a large scale, as in industrial applications, it is very difficult to obtain a highly purified polymer free of the monomer, because of the time-consuming and expensive purification processes. In the case of PDLLA synthesized by ring-opening polymerization of DL-lactide (DLLA), or

* To whom all correspondence should be addressed.

polycondensation of DL-lactic acid, it is almost inevitable that the as-polymerized product contains some amount of the monomer remaining unpolymerized, even if polymerization has been allowed to proceed to a monomer conversion as high as possible.

Because the hydrolytic degradation of polylactides takes place without the help of enzymes, even in the animal body, hydrolysis of PDLLA in this study was carried out in phosphate buffered solution (PBS) of pH 7·4 at 37°C in the absence of enzymes.

EXPERIMENTAL

DLLA polymers of lower molecular weights were prepared by polycondensation of DL-lactic acid, and those of higher molecular weights by bulk ring-opening polymerization of DL-lactide. DL-Lactide–glycolide copolymers (PLGA) were obtained by ring-opening copolymerization. All the polymerization procedures are similar to those described in a previous paper.[22] The polymerization conditions and characteristics of the resulting polymers are given in Table 1. Only PLA-7 and PLA-12 were obtained by polycondensation of DL-lactic acid, and all the others by ring-opening polymerization of DL-lactide. Films containing given amounts of DL-lactide monomer were prepared by adding the amounts of monomer to a 10 wt% chloroform solution of purified PDLLA with $\overline{M_w}$ of 42 600 (PLA-43), followed by casting and solvent drying. Polymer purification was conducted by repeated precipitation of polymers from 10 wt% chloroform solution with methanol. The thickness of the dried film was 500 µm. All other specimens were hot-pressed at 120°C and cut into strips 30 mm long, 2 mm wide and 0·5 mm thick.

Strips of specimens weighing approximately 0·5 g were immersed separately in 20 ml of PBS of pH 7·4 and conditioned in a water bath kept at 37 ± 0·5°C for hydrolysis. PBS was stirred at a rate of 30 rpm and exchanged for fresh PBS every week. Each strip was taken out after hydrolysis for a predetermined time, rinsed with distilled water, dried, and subjected to the following analyses.

The weight loss was calculated by comparing the dry weight (W_d) remaining after a predetermined hydrolysis time with the initial weight (W_i):

$$\text{Weight loss (\%)} = \frac{(W_i - W_d)}{W_i} \times 100$$

Water swelling and volume expansion of the hydrolysed specimens were evaluated from the weight and volume change before and after immersion in PBS.

Weight-average molecular weight ($\overline{M_w}$) of PDLLA was determined by gel permeation chromatography (GPC, Toyo Soda Co. Ltd., Tokyo, Japan) at 40°C using tetrahydrofuran (THF) as the mobile phase and calibrated using standard polystyrenes. The tensile strength of hydrolysed specimens was measured with a Tensilon UTM-II instrument manufactured by Toyo-Baldwin Co., Tokyo, Japan. Morphological change of the surface of fractured materials was observed with a scanning electron microscope (SEM) MSM-9 manufactured by Hidachi-Akashi Co., Tokyo, Japan, after freezing of the hydrolysed specimens in liquid nitrogen and fracturing.

RESULTS

PDLLA with added monomer

Following rigorous purification of DLLA polymerization products by repeated reprecipitation from chloroform solution with methyl alcohol, the PDLLA obtained was mixed with a given amount of DL-lactide monomer in chloroform solution and then cast on a glass plate to make a film with a thickness of 0·5 mm. Figure 1 shows the weight change of PLA-43 films observed when they were immersed in PBS at 37°C for different periods of time. The monomer content in the films ranged from 0 to 15 wt%. As can be seen, the

TABLE 1. Polymerization conditions and characteristics of homo- and co-polymers of DL-lactide (or DL-lactic acid) and glycolide

Polymer	DL-Lactide in		Polymerization		Conversion (%)	$\overline{M_w}$	T_g (°C)
	Monomer (wt%)	Copolymer (wt%)	Temp. (°C)	Time (h)			
PLA-7[a]	—	—	200	—	—	6 990	33
PLA-12[a]	—	—	240	—	—	11 540	35
PLA-43	100	100	160	3	98	42 600	51
PLGA-100	100	100	160	2	85	32 000	32
PLGA-66	75	66	160	3	96	38 400	39
PLGA-42	50	42	160	3	96	—	34
PLGA-27	25	27	160	3	96	—	35

[a] From DL-lactic acid.

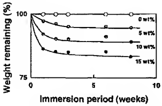

Fig. 1. Weight remaining after hydrolytic degradation of PLA-43 containing different contents of monomer.

weight change becomes very small after 3 weeks of immersion for all the films. The residual weight is 100, 95, 90 and 85 wt% of the initial weight for the films containing 0, 5, 10 and 15 wt% DL-lactide respectively. This result clearly indicates that almost all the monomer molecules added to the purified PDLLA were eluted from the films upon immersion in PBS for up to 8 weeks without polymer degradation, because no PDLLA fraction was lost during immersion in PBS at 37°C.

This was further confirmed by SEM observation on the remaining films. The SEM photographs of PLA-43 films taken after 1 week's immersion in PBS are shown in Fig. 2. It is apparent that the film which initially contained no monomer has no holes, in contrast to the films with added monomer. The round holes observed in these films suggest that the added monomer molecules existed in the PDLLA films as round clusters in a microphase-separated state, evenly distributed throughout the films.

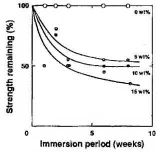

Fig. 3. Tensile strength remaining after hydrolytic degradation of PLA-43 containing different contents of monomer.

Figures 3 and 4 represent the change of mechanical strength and $\overline{M}_w$ of the PLA-43 films with monomer added after immersion in PBS. Obviously, the PDLLA film without monomer did not exhibit any decrease in

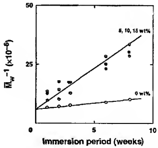

Fig. 4. $\overline{M}_w$ remaining after hydrolytic degradation of PLA-43 containing different contents of monomer.

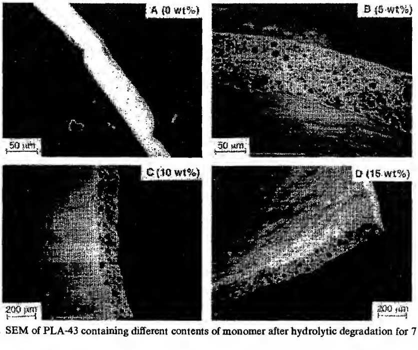

Fig. 2. SEM of PLA-43 containing different contents of monomer after hydrolytic degradation for 7 days.

mechanical strength and $\overline{M_w}$, with film immersed in PBS at 37°C up to 8 weeks. However, monomer addition to the PDLLA film strongly affected degradation of the polymer. The difference in the monomer content of the PDLLA films does not have a large effect on the decrease in strength or $\overline{M_w}$ in the range of monomer contents studied. The frequency of main-chain scissions of PDLLA molecules evaluated from the results shown in Fig. 4 was $6{\cdot}89 \times 10^{-5} \pm 1{\cdot}44 \times 10^{-5}$ repeating unit^{-1} day^{-1} for the films with monomer added and $9{\cdot}67 \times 10^{-6}$ repeating unit^{-1} day^{-1} for the purified PDLLA without monomer.

PDLLA as polymerized

We used three kinds of as-polymerized PDLLA products (PLA-7, PLA-12 and PLA-43). Two of them were obtained by ring-opening polymerization, and one by polycondensation of DL-lactic acid. Both the polymerizations were conducted to yield monomer conversions as high as possible, so that the residual monomer contents were very low. However, in the case of polycondensation, high monomer conversions were difficult to realize, because depolymerization of the polymer molecules formed could take place at high temperatures, as shown in a previous study.[22] The monomer conversion for the polymerizations which produced these PDLLA specimens is given in Table 1. The values are not correct in a strict sense because of the difficulty in clear separation of the residual monomer from the oligomeric PDLLA formed, especially for the polycondensation products.

Figure 5 shows the weight decrease of these as-polymerized PDLLA samples without any purification, plotted against the time of immersion in PBS. No quick weight decrease is observed in the early stages of contact with PBS for any of the three PDLLA specimens, in marked contrast with the PDLLA with monomer added shown in Fig. 1. Comparison of Fig. 5 with Fig. 1 reveals that the residual monomer content of as-polymerized polymers must be higher than 0% but lower than 5 wt%. Even the polycondensate (PLA-7) exhibits no initial quick weight decrease, but a continuous slow weight change with time. Apparently, PDLLA with lower $\overline{M_w}$ shows a faster weight decrease.

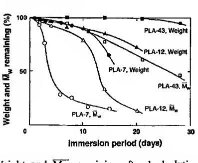

Fig. 5. Weight and $\overline{M_w}$ remaining after hydrolytic degradation of DL-lactide (or DL-lactic acid) homopolymers.

The results of SEM observation on these polymers after PBS immersion for different periods of time are shown in Fig. 6. It should be noted that the porous structure seen in Fig. 6 is substantially different from that in the SEM photographs for PDLLA with monomer added in Fig. 2. No large pores are noticed for the as-polymerized PDLLA with the highest $\overline{M_w}$ (PLA-43) even after 30 days of immersion in PBS, whereas the PDLLA with lower $\overline{M_w}$ have big pores ranging from 10 to 30 μm in diameter. The presence of these pores with large volume cannot be explained from the residual monomer content in the polymers. As readily anticipated from such porous structures, all the

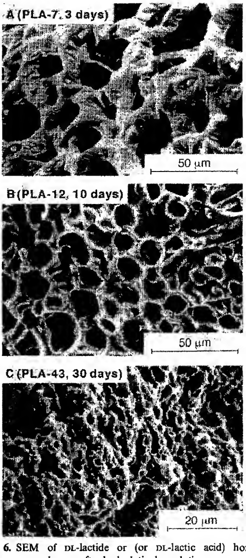

Fig. 6. SEM of DL-lactide or (or DL-lactic acid) homopolymers after hydrolytic degradation.

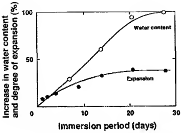

Fig. 7. Increase in water content and degree of expansion after hydrolytic degradation of PLA-43.

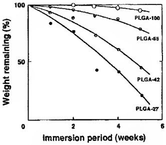

Fig. 10. Weight remaining after hydrolytic degradation of PLGA copolymers.

as-polymerized specimens were greatly swollen with water when immersed in PBS for a long period of time. As an example, the water content and volume expansion evaluated from the specimen weight and volume before and after drying are given in Fig. 7. It is likely that water can penetrate into PDLLA with time, resulting in volume expansion of the specimen. It should be pointed out that such large water swelling and volume expansion were not observed for the PDLLA with monomer added even when 15 wt% DLLA monomer was added to the purified polymer.

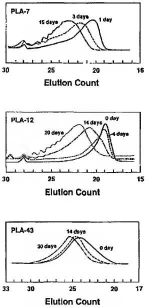

Fig. 8. GPC curves after hydrolytic degradation of DL-lactide (or DL-lactic acid) homopolymers.

The $\overline{M_w}$ and mechanical strength of the as-polymerized PDLLA decreased significantly with immersion time. The results are shown in Figs 8 and 9. The observed large decrease in $\overline{M_w}$ and strength for these specimens seems reasonable, because a large amount of water had diffused into the interior of the specimens, as demonstrated in Fig. 7.

PDLLA copolymerized with glycolide

In the case of DLLA homopolymerization, the polymerization products were contaminated physically, with the monomer remaining unpolymerized unless the product was subjected to purification. To study effects of the comonomer chemically incorporated into the PDLLA main-chain on the degradation of the resulting polymer, copolymerization of DLLA with glycolide was carried out and the polymerization products were rigorously purified by repeated reprecipitation. Therefore, it is highly probable that the copolymers are not contaminated with any residual monomer. The weight and molecular weight decrease of these purified copolymer

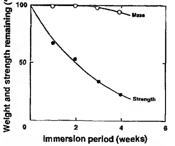

Fig. 9. Weight and tensile strength remaining after hydrolytic degradation of PLA-43.

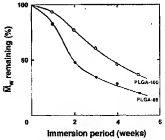

Fig. 11. $\overline{M_w}$ remaining after hydrophilic degradation of PLGA copolymers.

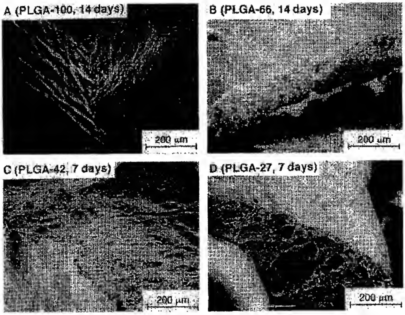

Fig. 12. SEM of PLGA copolymers after hydrophilic degradation.

specimens and their SEM photographs after immersion in PBS for different periods are shown in Figs 10, 11 and 12, respectively. As is well-known and seen in Fig. 10, chemical incorporation of glycolide units into DLLA polymer chains significantly accelerates the weight decrease of PDLLA. As a result of this degradation of the copolymers, the bulk phase of the specimens became porous, as shown in Fig. 12. Again, this porous structure is a little different from that of the PDLLA specimens with monomer added shown in Fig. 2, but similar to that of the as-polymerized polymers shown in Fig. 6.

DISCUSSION

As demonstrated in Figs 1 and 2, where the weight loss and SEM observed for mixtures of a purified DLLA polymer and with added monomer after PBS immersion are shown, the physically-added monomer seems to be readily extracted with PBS at 37°C. However, this does not mean that the presence of added monomer has no effect on the degradation of PDLLA, because a significant decrease in $\overline{M_w}$ and mechanical strength of these polymers was brought about by immersion in PBS, although the influence of the monomer content was not large in the range studied, as seen in Figs 3 and 4. On the contrary, the purified PDLLA with $\overline{M_w}$ of $4{\cdot}3 \times 10^4$ underwent virtually no degradation in PBS of pH 7·4 at 37°C during 8 weeks, suggesting that this PDLLA is highly resistant to hydrolysis unless residual monomer is contaminating the polymer. The reason for the significant degradation of PDLLA with added monomer, although most of the added monomer has been extracted in the early stages of PBS immersion, may be explained in terms of the residual monomer distribution as follows.

It is very likely that as-polymerized polymer products contain a trace or small amount of the monomer, even if polymerization has been conducted to practically 100% monomer conversion. The results shown in Figs 5–9 also support the presence of monomer in the polymerization products, because degradation of these polymers took place more markedly than that of the purified PDLLA as shown in Figs 1, 3 and 4. The difference in morphology observed in the SEM photographs between the as-polymerized PDLLA and specimens with monomer added immersed in PBS suggests that microscopic distribution of the monomer molecules in specimens with monomer added is different from that of the as-polymerized PDLLA. Probably, most of the monomer molecules added to the purified PDLLA polymer are dispersed as microphase-separated, small domains in the continuous matrix of the PDLLA, while the monomer molecules still remaining unpolymerized in the polymerization product may be almost molecularly and homogeneously distributed over the polymer matrix. When water diffuses into the PDLLA matrix from the outer PBS, the monomer in the PDLLA will be extracted or hydrolysed to $HOCH(CH_3)COOCH(CH_3)COOH$. This resulting acid will not only accelerate the water diffusion into the PDLLA matrix, but also act as a catalyst for the hydrolysis of PDLLA, although acid is a much weaker cata-

lyst of polylactides than base. Because the more homogeneously distributed monomer seems to be more effective in accelerating the hydrolysis of PDLLA, the as-polymerized products may undergo quicker degradation than the specimens with monomer added, even if the monomer content of as-polymerized products is lower than 5 wt%. This strongly suggests that the monomer remaining in polymerization products has to be removed as thoroughly as possible, if biodegradation of PDLLA products is required to take place more slowly and produce reproducible results. Otherwise, the PDLLA product would undergo unexpectedly quick degradation. Solvent molecules trapped in PDLLA products will also enhance polymer degradation if they are compatible with water.

The large effect of the initial $\overline{M_w}$ of PDLLA on the degradation seen in Figs 5 and 8 suggests that the end-groups of polymers affect the polymer degradation to a significant extent. If the number-average molecular weight of PDLLA is assumed to be $\overline{M_w}/2$, the content of end-groups expressed as wt% is equal to $2/\overline{M_w} \times 144 \times 100$, where 144 is the molecular weight of DL-lactide. Then the content of the end-groups of PLA-7, PLA-12 and PLA-43 amounts to 4·1, 2·5 and 0·7 wt%, respectively. Referring to the results shown in Figs 3 and 4, these contents of the end-groups are sufficiently high to affect the PDLLA degradation as a 'contaminating additive'.

The most conventional means to chemically incorporate additives into the main-chain of a polymer is to copolymerize with the additive monomer. The 'additive' incorporated by this copolymerization cannot be removed from the main-chain of the resulting copolymer by any purification. The degradation result for the DLLA copolymer with glycolide clearly indicates the enhancement of the incorporated glycolide unit on the copolymers. Indeed, copolymerization of DLLA with glycolide has been widely performed to enhance the degradation of PDLLA. It is well known that the ester bond in the glycolide is hydrolysed much faster than that of DL-lactide.

Finally it should be pointed out that in this study we used DLLA polymers, not L- and D-lactide polymers, because PDLLA is an amorphous polymer in contrast to PLLA and PDLA. Undoubtedly, the presence of crystalline regions in the matrix of biodegradable polymers offers another factor influencing the polymer degradation, making the degradation mechanism much more complicated than in their absence. This is the reason why we selected an amorphous polymer for this degradation study. As demonstrated above, even an amorphous polymer such as PDLLA displays a complicated mechanism of degradation in the presence of additives such as monomer, even if the additive content is less than a few weight percent.

In conclusion it should be stressed that reproducible degradation results will be obtained only when the starting polyester is purified to such an extent that any trace of additives (especially monomers that attract water or catalyse ester hydrolysis) is absent.

REFERENCES

1 Kulkarni, R. K., Moore, E. G., Hegyeli, A. F. & Leonard, F., *J. Biomed Mater. Res.*, **5** (1971) 169.
2 Brady, J. M., Cutright, D. E., Miller, R. A., Battistone, G. C. & Hunsuck, E. E., *J. Biomed. Mater. Res.*, **7** (1973) 155.
3 Cutright, D. E., Perez, B., Beasley, J. D., Larson, W. J. & Posey, W. R., *Oral Surg.*, 37 (1974) 142.
4 Miller, R. A., Brady, J. M. & Cutright, D. E., *J. Biomed. Mater. Res.*, **11** (1977) 711.
5 Reed, A. M. & Gilding, D. K., *Polymer*, **22** (1981) 494–498.
6 Hyon, S.-H., Jamshidi, K. & Ikada, Y., *Polymers as Biomaterials*, ACS Symposium Series, eds W. S. Shalaby *et al.* Plenum, New York, 1984, pp. 51–65.
7 Jamshidi, K., Hyon, S.-H., Nakamura, T., Ikada, Y., Shimizu, Y. & Teramatsu, T., *Biological and Biomechanical Performance of Biomaterials*, eds P. Christel, A. Meunier & A. J. C. Lee, Elsevier, Amsterdam, 1986, pp. 227–232.
8 Cam, D., Hyon, S.-H. & Ikada, Y., *Biomaterials*, **16**, (1995) 833–843.
9 Pitt, C. G., Gratzl, M. M., Kimmel, G. L., Surles, J. & Schindler, A. *Biomaterials*, **2** (1981) 215–220.
10 Li, S. M. Garrean, H. & Vert, M., *J. Mater. Sci. Mater. Med.*, **1** (1990) 198–206.
11 Conn, Jr, J., Oyasu, R., Welsh, M. & Beal, J. M., *J. Am. Surg.*, **126** (1974) 19.
12 Scholz, K. C., Lewis, Jr, R. C. & Bateman, R. O., *Surg. Gynecol. Obst.*, **135** (1972) 525.
13 Ruderman, R. J., Bernstein, E., Kairinen, E. & Hegyeli, A. F., *J. Biomed. Mater. Res.*, **7** (1973) 215.
14 Katz, A. R., Turner, R. J., *Surg. Gynecol. Obst.*, 133 (1970) 701.
15 Chu, C. C. & William, D. F., *J. Biomed. Mater. Res.*, **17** (1983) 1029.
16 Matlaga, B. F. & Salthouse, T. N., *J. Biomed. Mater. Res.*, **17** (1983) 185.
17 Fields, R. D., Rodriguez, F. & Finn, R. K., *J. Appl. Polym. Sci.*, **18** (1974) 3571.
18 Matsui, T., Nakamura, T., Tsuda, T., Lee, Y.-H. Shimizu, Y., Cha, W.-I., Hyon, S.-H., Ikada, Y. & Nishiya, K., *J. Jpn. Soc. Biomater.* **11** (1993) 330–337.
19 Tabushi, I., Yamada, H., Matsuzaki, H. & Furukawa, J., *J. Polym. Sci., Polym. Lett. Ed.*, **13** (1975) 447.
20 Williams, D. F. & Mort, E., *J. Bioeng.*, **1** (1977) 231.
21 Williams, D. F., *J. Biomed. Mater. Res.*, **14** (1980) 329.
22 Hyon, S.-H., Jamshidi, K. & Ikada, Y., *Biomaterials*, **18** (1997) 1503.
23 Gilding, D. K. & Reed, A. M., *Polymer*, **20** (1979) 1459–1464.
24 Pitt, C. G., Gratzl, M. M., Jefcoat, A. R., Zweidinger, R. & Schindler, A. *J. Biomed. Mater. Res.*, **13** (1979) 497.